REMARKS/ARGUMENTS

Reconsideration of the application in view of the above amendments and following remarks is requested. Claims 25-32 are now in the case. Claim 25 has been amended. No new matter has been added.

Support for amended claim 25 is found within the application as filed, such as at pages 3, 6, 14, and elsewhere.

Claims 25-32 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office believes that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse this ground of rejection.

The Office has alleged at pages 2-3 of the Office Action that applicants' specification "does not reasonably provide enablement [for] administration of a humanized antibody against the protein of SEQ ID NO:2 from amino acid residue 258 to residue 370 for reducing kidney fibrosis in a mammal." Applicants wish to point out that claim 27 is the only claim that recites the limitation "humanized." Support for this limitation is found within the specification at page 17 and elsewhere. Humanized antibodies are well known in the art and have been approved for therapeutic use in the United States since at least as early as 1998. See, Herceptin® package insert and approval letter, and Synagis® package insert, copies of which are enclosed. Thus, the production and use of humanized antibodies is within the level of ordinary skill in the art.

At page 3 of the Office Action, the Office has further characterized the claims as being drawn to the use of "a humanized monoclonal antibody." Applicants respectfully submit that no claim includes such a limitation; claim 26 recites that the antibody is a monoclonal antibody, and claim 27 recites that the antibody is a humanized antibody. To the extent that such antibodies are encompassed by the claims, Applicants believe that such subject matter is fully enabled. Production and use of humanized monoclonal antibodies is within the level of ordinary skill in the art. Both Herceptin® and Synagis® are humanized monoclonal antibodies as disclosed in their respective package inserts.

The Office has also alleged that zvegf4 is also known as PDGF-C, spinal cord-derived growth factor (SCDGF), and fallotein. Zvegf4 is not PDGF-C/SCDGF/fallotein. That protein is distinct from zvegf4, which is now known in the scientific literature as PDGF-D. See, applicants' specification at page 7, lines 1-2.

The amended claims are now limited to antibodies that are antagonists of zvegf4. In view of the evidence discussed herein, the specification enables one skilled in the art to use such antibodies to reduce kidney fibrosis in a mammal.

With regard to the state of the art, at page 4 of the Office Action the Office has cited Eitner and Floege, and Coppo and Amore as disclosing anti-PDGF-β as a treatment under development for fibrosis. The Office contends that "there is at best, only a general link between nephritis and cytokines." In fact, Eitner and Floege disclose a strong link between members of the PDGF family and kidney fibrosis. They state that "the platelet-derived growth factor (PDGF) family of cytokines is centrally involved in the mediation of glomerular mesangial cell, as well as tubulointerstitial myofibroblast cell, proliferation" and that "[t]he PDGF family may be a particularly attractive target when considering therapeutic options for treating renal fibrosis." (Page 257, right column.) Coppo and Amore also disclose a much stronger link between cytokines and glomerulonephritis than the Office acknowledges. In the Abstract, the authors state, "Interest has recently focused on anti-inflammatory cytokines (monoclonal antibodies, peptidic antagonists or anti-sense oligonucleotides agains TNF-α, anti-PDGF-β, anti-TGF-β and cytokine receptor antagonists) and anti-inflammatory natural cytokines (such as IL4, IL10, IL13 or low doses of TGFβ)." At page 261, left column, second paragraph they disclose that cytokine antagonists have been found to be useful in experimental glomerulonephritis. These disclosures thus demonstrate that the art recognizes a causative link between cytokines and kidney fibrosis and also recognizes the utility of cytokine antagonists as therapeutics for fibrotic diseases of the kidney. Other art of record, including Johnson et al., *J. Exp. Med.* 175:1413-1416, 1992 (Ref. A17 in applicant's Information Disclosure Statement of Oct. 1, 2003) and Yagi et al., *Gen. Pharmac.* 31:765-773, 1998 (Ref. A35) disclose a link between members of the PDGF family and glomerulonephritis, including the inhibition of fibrosis in animal models using antagonists of the PDGF-PDGF receptor pathway. In summary, it is believed that the cited disclosures, when read in light of applicants' data, support applicants' assertion of enablement.

Applicants have disclosed experimental data showing that overexpression of zvegf4 in an animal results in proliferative glomerulopathy, a fibroproliferative disorder of kidney (specification at pages 37-38). These results demonstrate that zvegf4, like previously studied members of the PDGF family, can cause kidney fibrosis.

With regard to the predictability in the art, applicants have established a nexus between elevated levels of zvegf4 and kidney fibrosis. Further evidence of a causal relationship between zvegf4 expression and the development of fibroproliferative disorders of kidney is provided in the enclosed Declaration of Debra G. Gilbertson Under 37 C.F.R. § 1.132. That evidence includes *in vitro* activity of zvegf4 on renal cells that play a major role in disease development; additional *in vivo* studies comparing the effects of overexpression of zvegf4 and other PDGF family members; and the expression of zvegf4 and its receptor in fibrotic areas of diseased human kidneys. Ms. Gilbertson concludes that these data provide

support for a causal role of zvegf4 in the pathogenesis of fibroproliferative kidney disease and for the use of zvegf4 antagonists in the treatment of kidney disease.

The Office has also asserted that the amount of guidance given by the specification is insufficient, alleging, *inter alia*, that details of antibody administration and contraindications "are virtually non-existent." Applicants respectfully disagree with the Office's characterization of their disclosure and with the level of detail the Office appears to be requiring. One of ordinary skill in the art would recognize that the term "reduce kidney fibrosis" indicates at least a statistically significant reduction in disease progression as compared to an untreated patient. See, specification at page 6, lines 15-18 and page 21, lines 18-21. Such a determination is within the level of skill in the art. As to the route of administration, the Office's attention is directed to applicants' specification at page 22, lines 3-19, wherein routes of administration, as well as criteria for determining dose, are disclosed. Antibody therapeutics are ordinarily administered by infusion or injection. See the enclosed package inserts. Clinical endpoints are disclosed in the specification at pages 6 and 21. Applicants respectfully submit that there is no requirement that an applicant for patent disclose contraindications for a therapeutic. Product safety is the province of the FDA. See, MPEP2164.05(a) ("However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled.") and MPEP 2164.01(c) ("The applicant need not demonstrate that the invention is completely safe.").

Administration of therapeutic antibodies is now routine in the art. Applicants respectfully submit that sufficient guidance with regard to dose and method of use have been provided. See, MPEP 2164.01(c):

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. . . . For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

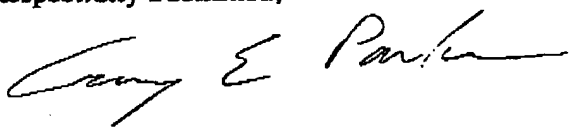
Moreover, it is axiomatic that a patent need not disclose what is well known in the art. Enablement must be judged in light of the state of the art, which includes the therapeutic use of monoclonal antibodies against cytokines and their receptors. Applicants have disclosed sufficient information regarding clinical endpoints, dose determination, and route of administration to enable one of ordinary skill in the art to carry out the invention without undue experimentation.

In view of the above amendments and arguments, it is believed that the rejection under Section 112, first paragraph, has been overcome. Reconsideration and withdrawal of the rejection are requested.

At line 2 of page 4 of the Office Action, the Office has referred to "Appendix A—MeSH database printout" but no copy of this document has been provided, nor has it been listed on the Form PTO-892 included with the Office Action. If the Office continues to rely on this disclosure, it is requested that a copy be provided to applicants.

Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,



Gary E. Parker
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Enclosures:

Amendment Fee Transmittal (in duplicate)
Declaration of Debra G. Gilbertson Under 37 C.F.R. § 1.132
3 References

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